Notice of Allowability	Application No.	Applicant(s)	
	10/759,600	DALE, JAMES B.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Applicant's amendment filed 01/03/07*.

2. ☒ The allowed claim(s) ~~is~~/are *claims 1-24, 28 and 30, the latter two renumbered as claims 25 and 26 respectively*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 011604
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

ATTACHMENT TO NOTICE OF ALLOWABILITY

Preliminary Amendments

1) Acknowledgment is made of Applicant's preliminary amendments filed 08/31/06 and 01/16/04.

Election

2) Acknowledgment is made of Applicant's election filed 01/03/07 in response to the restriction requirement mailed 10/03/06. Applicant has elected species (A), a method that uses a bivalent recombinant fusion polypeptide, and the Group A streptococcal serotype M24 species. However, due to the lack of prior art on the elected species, the non-elected recombinant fusion polypeptide species (B), (C) and (D) and all of the streptococcal serotype species have also been fully searched and examined. The species election requirement set forth in the instant application is hereby withdrawn.

Examiner's Amendment

3) An Examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to Applicant, an amendment may be filed as provided by 37 C.F.R 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee. The authorization to prepare this Examiner's amendment was provided by Ms. Mae Rosok in a telephonic interview on 28 March 2007. Ms. Rosok stated that she is agreeing to cancel claims 25-27, 29 and 31-51 without acquiescence.

This application has been amended as indicated below.

(a) The first paragraph of the instant specification is replaced with the following: --CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional of U.S. Patent Application No. 09/159,409, filed September 10, 1998, now U.S. Patent 6,716,433, which application claims the benefit of United States Provisional Application No. 60/058,635, filed September 12, 1997, which applications are incorporated by reference in their entirety.--

(b) The paragraph bridging pages 21 and 22 of the instant specification has been replaced with the replaced with the following:

--To assure that none of the M protein vaccines evokes tissue-crossreactive antibodies, indirect immunofluorescence assays are performed using frozen sections of human heart, kidney, and brain (Dale, J.B. and Beachey E.H., "Protective antigenic determinant of streptococcal M protein shared with sarcolemmal membrane protein of human heart," *J. Exp. Med. 156*:1165-1176, 1982). Thin sections of tissue obtained at autopsy (4um) are prepared on microscope slides and stored in a sealed box at -70°C until use. Test serum is diluted 1:5 in PBS and dropped onto the tissue section. Control slides are made with preimmune serum and PBS. The slides are incubated at ambient temperature for 30 minutes and then washed three times in PBS in a slide holder. Fluorescein-labeled goat anti-IgG/IgM/IgA is diluted 1:40 in PBS and dropped onto the slides which are again washed, dried, and mounted with 1% ~~Gelvetol~~ GELVETOL and a coverslip. Fluorescence is detected using a Zeiss Axiophot microscope equipped with a xenon light source. Immunofluorescence is recorded using a scale of 0-4+, with 0 being no fluorescence and 4+ being that obtained with a standard, positive antiserum raised in rabbits against whole type 5 M protein (Dale, J.B. and Beachey, E.H., "Multiple heart-cross-reactive epitopes of streptococcal M proteins," *J. Exp. Med. 161*:113-122, 1985).--

(c) The paragraph beginning at page 9, line 3 has been replaced with the following paragraph:

--Expression vectors transfected into prokaryotic host cells generally comprise one or more phenotypic selectable markers such as, for example, a gene encoding proteins that confer antibiotic resistance or that supplies an auxotrophic requirement, and an origin of replication recognized by the host to ensure amplification within the host. Other useful expression vectors for prokaryotic host cells include a selectable marker of bacterial origin derived from commercially available plasmids. This selectable marker can comprise genetic elements of the cloning vector pBR322 (ATCC 37017), Briefly, pBR322 contains genes for ampicillin and tetracycline resistance and thus provides simple means for identifying transformed cells. The pBR322 "backbone" sections are combined with an appropriate promoter and a mammalian ETF structural gene sequence. Other commercially available vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden), pQE30 ~~(His-tag expression vector)~~ (6xHis-tag expression vector), and pGEM1 (Promega Biotec, Madison, WI, USA).--

(d) The paragraph bridging pages 16 and 17 of the specification has been replaced with the following paragraph:

--A. Purification

Transformed *E. coli* were grown in a shaking incubator to log phase in 11 of LB containing 100 lag/ml ampicillin and 25 μg/ml kanamycin. IPTG (2 mM) was added for the final four hours of growth. The cell pellet was suspended in 30 ml PBS and lysed in a French pressure cell at 1000 psi. The hexavalent protein was purified from the supenatant using nickel nitrilotriacetic acid (Ni-NTA) ~~Ni-NTA~~ resin according to the protocol provided by the manufacturer (Qiagen, Valencia, CA). The elution buffer containing the protein was concentrated from 15 ml to 5 ml in a spin filter (ULTRAFREE®-15, Millipore). Final purification was accomplished by gel filtration over SUPERDEX™ 75 (prep grade, Pharmacia Biotech). The active fraction was identified by Western blots (Dale, J.B. and Beachey, E.H., "Multiple heart-cross-reactive epitopes of streptococcal M proteins," *J. Exp. Med. 161*:113-122, 1985) using rabbit antiserum against pep M24 (Beachey et al., "Purification and properties of M protein extracted from group A streptococci with pepsin: Covalent structure of the amino terminal region of the type 24 M antigen," *J. Exp. Med. 145*:1469-1483, 1977). Total protein concentration was determined by standard methods and the sample was diluted in PBS to contain 200 μg/ml of hexavalent protein. Purity of the samples was determined by gel scanning (PHOTOSHOP™ digital image and COLLAGE™ image analysis).--

(e) Claims 1, 3, 5, 14-17, 20-22, 24, 28 and 30 have been amended as indicated below:

--Claim 1 (Currently amended). A method for eliciting an immune response against Group A streptococci[[,]] comprising administering to a patient a pharmaceutical composition comprising (a) a recombinant fusion polypeptide wherein said recombinant fusion polypeptide comprises a multivalent immunogenic portion fused to an immunogenic polypeptide carboxy-terminal to the multivalent immunogenic portion, which protects the immunogenicity of the multivalent immunogenic portion, wherein the multivalent immunogenic portion comprises at least two immunogenic amino-terminal polypeptides of Group A streptococcal M protein from at least two different Group A streptococcal serotypes, wherein the immunogenic polypeptide carboxy-terminal to the multivalent immunogenic portion is a reiteration of the immunogenic

amino-terminal polypeptide from the amino terminus of the multivalent immunogenic portion, and wherein each of the at least two immunogenic amino-terminal polypeptides is at least 10 amino acids in length, and (b) a pharmaceutically acceptable excipient, carrier, stabilizer or diluent, thereby eliciting [[an]] said immune response against said Group A streptococci.--

--Claim 3 (Currently amended). The method according to claim 1 wherein the multivalent immunogenic portion of the fusion polypeptide ~~comprises~~ consists of six immunogenic amino-terminal polypeptides of Group A streptococcal M protein from six different Group A streptococcal serotypes.--

--Claim 5 (Currently amended). The method according to claim 1 wherein the multivalent immunogenic portion of the fusion polypeptide ~~comprises~~ consists of ten different Group A streptococcal serotypes.--

--Claim 14 (Currently amended). The method according to any one of claims 1 to 3 wherein the administered ~~fusion polypeptide~~ composition elicits an immune response comprising opsonic antibodies against Group A streptococcal M protein that do not cross-react with human tissue.--

--Claim 15 (Currently amended). The method according to claim 1 wherein the recombinant fusion polypeptide further comprises a selectable marker encoded by an expression vector.--

--Claim 16 (Currently amended). The method according to claim 15 wherein the expression vector is a 6xHis-tag vector.--

--Claim 17 (Currently amended). The method according to claim 16 wherein the selectable marker binds to nickel nitrilotriacetic acid (Ni-NTA) resin.--

--Claim 20 (Currently amended). The method according to claim 1 or claim 19 wherein the ~~recombinant fusion polypeptide~~ composition is administered via [[a]] subcutaneous route, [an]] intramuscular route, or [[a]] mucosal route.--

--Claim 21 (Currently amended). The method according to claim 20 wherein the ~~recombinant fusion polypeptide~~ composition is administered via [[an]] the intramuscular route to ~~a human~~ said patient at a concentration of 50 μg to 300 μg.--

--Claim 22 (Currently amended). The method according to any one of claims 1 to 3 wherein the ~~recombinant fusion polypeptide is~~ composition further ~~formulated with~~ comprises an adjuvant.--

--Claim 24 (Currently amended). The method according to claim 22 wherein the ~~recombinant fusion polypeptide is~~ composition further ~~formulated with~~ comprises an immunomodulatory cofactor.--

--Claim 28 (Currently amended). The method according to claim ~~25~~ 1 or claim ~~26~~ 22 wherein the ~~pharmaceutically acceptable excipient, carrier, stabilizer or diluent,~~ composition comprises at least one of a buffer, antioxidant, carbohydrate, and chelating agent.--

--Claim 30 (Currently amended). The method according to claim ~~29~~ 24 wherein the immunomodulatory cofactor is selected from the group consisting of IL-4, IL-10, γ-IFN, IL-2, IL-12, and IL-15.--

Status of Claims

4) Claims 1, 3, 5, 10 and 25 have been amended via the amendment filed 01/03/07.

Claims 25-27, 29 and 31-51 have been canceled via this Examiner's amendment.

Claims 1, 3, 5, 14-17, 20-22, 24, 28 and 30 have been amended via this Examiner's amendment.

Claims 1-24, 28 and 30 are pending and are under examination.

Information Disclosure Statement

5) Acknowledgment is made of Applicant's information disclosure statement filed 01/16/04. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Sequence Listing

6) Acknowledgment is made of Applicants' raw Sequence Listing which has been entered 01/29/04.

Priority

7) The instant application is a divisional of application SN 09/151,409, filed 09/10/1998, now US patent 6,716,433, which claims priority to the provisional application 60/058,635, filed 09/12/1997.

Drawings

8) Acknowledgment is made of Applicant's drawings filed 01/16/04, which have been accepted.

Reasons for Allowance

9) The following is an examiner's statement of reasons for allowance:

Instant claims are drawn to a method of using a composition comprising the recombinant fusion polypeptide claimed in US patent 6,716,433. The claimed method of eliciting an immune response against Group A streptococci comprising administering to a patient a pharmaceutical composition comprising the recited recombinant fusion polypeptide, is free of prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Remarks

10) Claims 1-24, 28 and 30 are allowed. Claims 28 and 30 have been renumbered as claims 25 and 26 respectively.

The amendments made to the claims via this Examiner's amendment have descriptive support in the specification as originally filed.

The amendments made to claim 1 are supported by the canceled claim 25, first full paragraph under 'Summary of the Invention' on page 2; last full paragraph of page 4; and paragraph bridging pages 12 and 13 of the specification as filed.

The amendment made to claims 3 and 5 is supported by the original claims 3 and 5; lines 3-5 on page 8; and Figure 1 of the specification.

The replacement of the limitation 'His-tag vector' with --6xHis tag vector-- in claim 16 and in the first paragraph of page 9 of the specification does not constitute new matter. In the parent application, 09/151,409, Applicant showed that pQE30 vector described at line 14 of page 9 and line 12 of page 17 of the instant specification was known in the art as --6xHis-tag vector-- by submitting an article entitled 'Ni-NTA resins – your key to efficient purification of 6xHis-tagged proteins' from *Qiagen News*, Issue 4, 1-5, 1997; and Qiagen documents entitled 'pQE-30,

pQE-31, and pQE-32 Vectors'; and 'QIAexpress®: The Complete System for 6xHis Technology', 1-31, 06/2000.

The replacement of the limitation 'nickel resin' with --nickel nitrilotriacetic acid (Ni-NTA) resin-- in claim 17 and in the paragraph bridging pages 16 and 17 of the specification does not constitute new matter. In the parent application, 09/151,409, Applicant showed that it was well known in the art at the time of the invention that the abbreviation Ni-NTA was the standard abbreviation used for 'nickel nitrilotriacetic acid' by submitting an article entitled 'Ni-NTA resins – your key to efficient purification of 6xHis-tagged proteins' from *Qiagen News*, Issue 4, 1997.

11) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Central Fax number, (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

12) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

13) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

March, 2007

S. DEVI, PH.D.
PRIMARY EXAMINER